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REMARKS

I. Status of Application

Claims 1-5, 7, and 11-44 are currently presented to the Examiner. Claims 1-5 and 7 are amended herewith. Claim 8 is cancelled herewith. Claims 11-44 are added as new claims. Claims 1-5 and 7 stand rejected under 35 U.S.C. 102(b) as being anticipated by Showa Denko KK JP 62096408. Applicant respectfully traverses the rejection and requests withdrawal of the same. In light of Applicant's June 18, 2003 Amendment and Response, the Examiner has withdrawn her rejection of Claims 1-4 and 7-10 under 35 U.S.C. § 102(b) as anticipated by Lion Corporation, JP 8099849 and her rejection of Claims 1-6 rejected under 35 U.S.C. § 102(b) as anticipated by Lion Corporation, WO 02/02124.

Applicant has amended the claims to more clearly define and distinctly characterize Applicant's novel invention. Specifically, claim 1 has been amended to reinstate the term "carrier" for "denture adhesive" and has further added a limitation to the composition that includes a "tartar control agent." Support for the addition of a "tartar control agent" can be found in the specification at least at page 5, lines 21-25, page 6, lines 26- 29, page 13, lines 7-15, and page 15, lines 1-9. The amendments presented herein add no new matter.

Applicant has obtained official translations of Showa Denko KK JP 62096408 and Lion Corporation, JP 8099849 from Burg translations, copies of which are enclosed with this response. Further, because Applicant has amended the claims to reinstate the "carrier" limitation, Applicant addresses herein the rejections of the claims over Lion Corporation, JP 8099849 and Lion Corporation, WO 02/02124.

Applicant respectfully requests entry and consideration of the foregoing amendments and remarks, which are intended to place this case in condition for allowance.

II. The Pending Claims are Novel over Showa Denko KK JP 62096408

In the present Office Action, the Examiner maintains and repeats the rejection of claims 1-5 and 7-8 as stated at page 2, paragraph 1 of the December 18, 2002 Office Action, as rejected under 35 U.S.C. § 102(b) as being anticipated by Showa Denko KK, JP 62096408 (the AG abstract). The Examiner is of the opinion that the AG abstract teaches ascorbic acid phosphoric acid ester or its salt (Na, K, Ca or Mg salt) in an oral composition to be used for alveolar pyorrhea, cleaning teeth, removing bad breath and washing the teeth. The Examiner further asserts that the compositions of the AG abstract can be in the form of a toothpaste, chewing gum or troche. The Examiner admits that "It is not clear from the abstract provided that the agent contains all the optional agents of instant claim 8. It is clear that it is used orally in a composition and since these are usual agents in compositions such as toothpaste, instant claim 8 is included in the rejection. This can be amended with a more complete translation of the document." Original claim 8 recited, *inter alia*, a composition comprising an ascorbyl phosphate compound and a carrier "which optionally includes one or more of an anticaries agent, a tartar control agent, an antimicrobial agent, and a desensitizing agent."

Applicant respectfully traverses this rejection. Applicant respectfully submits that for a reference to anticipate a claim, the reference must teach each and every element of the claim.

Applicant's amended claims are directed to an oral care composition comprising an orally acceptable carrier, an ascorbyl-2-phosphate compound having the structure set forth in claim 1, or a sodium or potassium salt thereof, and a tartar control agent. Applicant's claimed composition is useful for assisting in the reduction or prevention of tartar formation on the teeth (page 13, lines 8-10), and is beneficial for scavenging free radicals present in the oral cavity to reduce or eliminate the potential effects of reactive oxygen species (page 6, lines 2-5).

As indicated above, Applicant has obtained a translation of Showa Denko KK, JP 62096408 ("Showa Denko"). Showa Denko teaches L-ascorbic acid-2-phosphate compositions that are useful for preventing and treatment of periodontosis, cleaning the oral cavity, elimination of halitosis, and freshening of the mouth. Nowhere does the AG abstract teach or suggest an ascorbyl-2-phosphate composition including a tartar control agent, nor does the Showa Denko teach Applicant's claimed oral care composition comprising a carrier and a tartar control agent combined with an ascorbyl-2-phosphate compound. Thus, Showa Denko fails to anticipate Applicant's invention.

Accordingly, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 102(b) as anticipated by Showa Denko be reconsidered and withdrawn.

III. The Pending Claims are Novel over Lion Corp., JP 8099849

At page 3, paragraph 2 of the December 18, 2002 Office Action, claims 1-4 and 7-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lion Corp., JP 8099849. This rejection was withdrawn in the October 1, 2003 Office Action; however, Applicant addresses the patentability of the amended claims over JP 8099849 herein.

Applicant respectfully traverses this rejection. Applicant respectfully submits that, for a reference to anticipate a claim, the reference must teach each and every element of the claim.

As indicated above, Applicant has obtained a translation of JP 8099849, which is directed to a composition for an oral cavity comprising an ascorbic phosphate ester and one or more of menthone, carvone, cineol, limonene, menthane, anethole, eugenol, and cinnamaldehyde, and menthol. JP 8099849 teaches that such compositions provide high protective and therapeutic effects with respect to periodontal diseases by improving the active oxygen elimination effects of ascorbic phosphate ester and by improving absorption thereof in gingival tissues. Antimicrobial agents, enzymes, fluorides, and water-soluble inorganic phosphoric acid compounds may be

blended with these compositions. Nowhere does JP 8099849 teach or suggest compositions which comprise tartar control agents, let alone teach Applicant's claimed oral care composition comprising an ascorbyl-2-phosphate compound combined with a tartar control agent. Thus, JP 8099849 fails to anticipate Applicant's invention.

IV. The Pending Claims Are Novel Over Lion Corporation, WO 2002 02124 A1

At page 3, paragraph 3 of the December 18, 2002 Office Action, claims 1-6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lion Corporation, WO 2002 02124 A1 (the BS abstract). This rejection was withdrawn in the October 1, 2003 Office Action; however, Applicant addresses the patentability of the amended claims over the BS abstract herein. The Examiner is of the opinion that the BS abstract teaches compositions containing ascorbic acid phosphoric acid esters or its salts comprising a surfactant, one or more sugar alcohols and a calcium and aluminum ion source. The Examiner further asserts that the composition set forth in the BS abstract appears to be an oral composition that would be mixed with saliva.

Applicant respectfully traverses this rejection. Applicant respectfully submits that the BS abstract is not prior art to the claimed invention. The present invention claims priority to U.S. Provisional Appl. No. 60/263,884, filed January 24, 2001, which includes subject matter relating to ascorbyl-2-phosphate compound combinations with tartar control agents and which predates the filing date of March 27, 2001 for WO 2002 02124. *See* MPEP 2136. Applicant has enclosed a copy of U.S. Provisional Appl. No. 60/263,884 to evidence this disclosure.

Further, even if the BS abstract is considered prior art, Applicant respectfully submits that for a reference to anticipate a claim, the reference must teach each and every element of the claim.

The BS abstract is directed to compositions containing ascorbic acid phosphoric acid esters. The abstract shows drawings of teeth, but it contains no language specifically teaching

compositions suitable for oral use. The abstract certainly fails to teach or suggest tartar control agents in general, and provides no teaching of Applicant's claimed oral care composition comprising an ascorbyl-2-phosphate compound combined with a tartar control agent. Thus, the BS abstract fails to anticipate Applicant's invention.

V. Conclusion

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1-5, 7, and 11-44 are in condition for allowance.

None of Applicant's amendments or cancellations are to be construed as dedicating any such subject matter to the public, and Applicant reserves all rights to pursue any such subject matter in this or a related patent application.

It is respectfully submitted in view of the foregoing Amendment and Remarks that all of the objections and rejections in the Office Action dated October 1, 2003 have been overcome and should be withdrawn. Applicant respectfully requests early and favorable notification to that effect. The Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully submitted,

By: Christine M. Rebman
Christine M. Rebman
Reg. No. 50,546

MAYER, BROWN, ROWE & MAW LLP
P.O. Box 2828
Chicago, Illinois 60690-2828
Telephone: (312) 701-7174
Facsimile: (312) 706-8361

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(54) Title of the Invention: DRUG FOR ORAL CAVITY

(21) Application No. Sho 60-235451

(22) Filing Date: October 23, 1985

(72) Inventor: ITO, Shinobu

c/o Showa Denko K.K., 1-13-9 Shiba-Daimon, Minato-ku, Tokyo

(72) Inventor: OGATA, Eiji

c/o Showa Denko K.K., 1-13-9 Shiba-Daimon, Minato-ku, Tokyo

(71) Applicant: Showa Denko K.K., 1-13-9 Shiba-Daimon, Minato-ku, Tokyo

(74) Agent: Seiichi Kikuchi, Patent Attorney

Specification

[Translator's note: Additions and deletions based on an attached page of amendments filed by the applicant Showa Denko and dated December 27, 1985, are incorporated in the translated text and indicated by the "track changes" function (deleted original text is struck out and new text underlined).]

1. Title of the Invention

Drug for Oral Cavity

2. Claims

A drug for the oral cavity characterized as containing an L-ascorbic acid-2-phosphate or a salt thereof as an active ingredient.

3. Detailed Description of the Invention

(Industrial Field of Application)

The present invention relates to a drug for the oral cavity that is effective for the prevention and treatment of periodontosis, cleaning of the oral cavity, elimination of halitosis, and freshening of the mouth, and contains a stable derivative of ascorbic acid.

(Prior Art and Related Problems)

Ascorbic acid strengthens capillary vessels by aiding the production of mucopolysaccharides contained in the connective tissue, and strengthens the oral cavity structure by contributing to the hydration of proline and stimulating the production of collagens. It further manifests an antimicrobial action on bacteria in the oral cavity that are a cause of plaque, which contributes tooth decay and gum disease.

Nevertheless, since ascorbic acid is a strongly reductive substance and is easily oxidized, losing its effect and producing marked discoloration, it has been extremely difficult to adapt as a drug for the oral cavity.

In light of these circumstances, the present inventors, as the result of intensive and varied research aimed at obtaining a drug for the oral cavity that has sufficient activity of ascorbic acid but is also extremely stable; found that L-ascorbic acid-2-phosphates and their salts are suitable as drugs for the oral cavity.

(Constitution of the Invention)

Specifically, the present invention provides a drug for the oral cavity containing as its effective ingredient an L-ascorbic acid-2-phosphate or a salt thereof, such as a sodium, potassium, calcium, or magnesium salt.

L-ascorbic acid-2-phosphates and their salts are both safe and extremely stable, readily dissolve in water, and exhibit excellent effect in the prevention and treatment of periodontosis, since the effects of ascorbic acid are sufficiently manifested when the compound is used in the living body.

The oral composition of the present invention may be used in various forms of dosage form such as toothpaste, powder or liquid, or can be formulated in other forms such as chewing gum, paste, gargle, or troche.

The amounts blended vary according to the formulation and therefore cannot be uniformly prescribed, but generally is appropriate to contain this ingredient in the amount of 0.01 to 10% (wt.%). While there is no strict limitation with respect to the amount used in effective ingredient conversion, normally, 0.1 to 5 g per day is appropriate, and can be increased or decreased as necessary.

Next, representative working examples of the present invention are described, but of course

the present invention is not restricted to these examples alone.

Working Example 1

A toothpaste was prepared by normal methods in accordance with the following recipe:

Ingredients	Wt %
calcium diphosphate dihydrate	45.0
sodium carboxymethylcellulose	0.5
carrageenan	0.5
glycerin	10.0
sorbitol	10.0
fragrance	1.0
preservative	0.1
sodium saccharin	0.1
sodium lauryl sulfate	2.0
sodium chloride	2.0
ascorbic acid magnesium phosphate	1.0
water	remainder

Working Example 2

A gargle was prepared by normal methods in accordance with the following recipe:

Ingredients	Wt %
95% ethyl alcohol	35.5%
glycerin	14.0%
fragrance	1.0%
ascorbic acid magnesium phosphate	1.0%
water	remainder

Working Example 3

A troche was prepared by normal methods in accordance with the following recipe:

Ingredients	Wt %
white sugar	85.0%
magnesium stearate	1.0%
high propyl cellulose	8.0%
menthol	trace
ascorbic acid magnesium phosphate	3.0%

Working Example 4

A chewing gum was prepared by normal methods in accordance with the following recipe:

Ingredients	Wt %
gum base	65.0%
mannit	20.0%
fragrance	2.0%
70% sorbit	3.0%
ascorbic acid magnesium phosphate	1.0%

(Effect of the Invention)

(1) Safety Test

The safety of an oral composition containing L-ascorbic acid-2-phosphate was confirmed using SD rats five weeks of age. The oral composition used was prepared in accordance with the method of Working Example 1 described above.

30 rats having an average weight of 131.2 g were divided into two groups. The oral composition of Working Example 1 was administered to one group, while the same oral composition of Working Example 1 described above without L-ascorbic acid-2-phosphate was administered to the other group orally twice a day for 10 days. After 11 days the rats were sacrificed, tissue was removed from the gums and mucous membrane and saliva glands from the oral cavity of the rats among and tissue fragments were observed by microscope using normal methods. As a result, it was confirmed that no pathological changes occurred in the tissue in comparison with the 15 animals in the contrast group, to which L-ascorbic acid-2-phosphate was not administered.

(2) Stability Test

Next, the stability of various oral compositions containing L-ascorbic acid-2-phosphate was studied, and the results are shown.

The oral compositions used were prepared in accordance with the recipe of Working Example 1 described above. The oral compositions were each store at 50°C for 10 days, 20 days and 30 days, and discoloration was evaluated in accordance with the following standards.

A: no discoloration, B: slight discoloration, X: marked discoloration

The results are shown in Table 1.

(Table 1) Change in the color of oral compositions containing L-ascorbic acid-2-phosphate at 50°C

		10 days	20 days	30 days
L-ascorbic acid-2 magnesium phosphate 10%		B	B	B
		A	A	B
	5%	A	A	A
	3%	A	A	A
ascorbic acid	1%	X	X	X
	10%	B	X	X
	5%	B	X	X
	3%	B	B	X
	1%	A	A	A
Not added (contrast group)				

As is shown in Table 1, the oral composition to which L-ascorbic acid-2-phosphate was added was highly stable and extremely resistant to discoloration even when ascorbic acid was added.

In addition, precisely 50 mg ascorbic acid magnesium phosphate was dissolved in 100 ml water, and the aqueous solution obtain was allowed to stand for 30 days, and changes in the L-ascorbic acid-2-phosphate were followed by high-speed liquid chromatography, but even after 30 days the amount of ascorbic acid magnesium phosphate showed little change, and it was confirmed that ascorbic acid magnesium phosphate is extremely stable in an aqueous solution.

The high-speed liquid chromatography performed was measured on the following conditions using the JASCO UV-DEC 100 manufactured by JASCO.

Column: Shodex OH pak Q-801

Elution liquid: (Na₂SO₄ 0.05 mol/H₃PO₄ 0.05 mol)/L

Flow rate: 0.7 ml/min Detection method: UV 257 nm

Pressure: 8 kg/cm²

(3) Efficacy Test

20 patients (males aged 25 to 45 years) having various periodontal diseases such periodontosis and marginal gingivitis were divided into two groups of 10 patients each, with patients with the same degree of symptoms evenly distributed between the two groups. One of the groups was treated for 60 days twice a day, in the morning and evening, with the oral composition containing ascorbic acid magnesium phosphate in accordance with the recipe of Working Example 1 described above. The other group used as a control was treated with an oral composition (2 g) having the same recipe as in Working Example 1 described above but not containing ascorbic acid magnesium phosphate.

As an indicator of efficacy, in the event of improvement of one item among the pathological fluctuation and relaxation, bleeding, pathological gingival [illegible] formation, gingival discoloration, retraction of the gums, severe halitosis, one point was awarded, and the number of points was tabulated for improvement of multiple items.

On the other hand, in the case of aggravation of symptoms among the aforesaid items, minus one point was awarded, and in the case of no change, zero points were awarded, and the final number of points for each patient was tabulated.

The results are shown in Table 2. The value shown by the total points divided by the number of patients.

(Table 2)

	10 days	20 days	30 days	40 days	50 days	60 days
Oral composition containing L-ascorbic acid-2-phosphate	+0.4	+0.9	+0.6	+1.2	+1.5	+1.7
Contrast group: Oral composition not containing L-ascorbic acid-2-phosphate	-0.5	-0.3	-0.3	-0.4	-0.3	-0.2

It is clear from the results in Table 2 that the oral composition containing the ascorbic acid phosphate was extremely efficacious against periodontal diseases.

Applicant: Showa Denko K.K.

Translation from Japanese

- (12) OFFICIAL GAZETTE FOR UNEXAMINED PATENT APPLICATIONS (A)
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- (71) Applicant: Lion Corp. (000006769)
 3-7 Honjo 1-chome, Sumida-ku, Tokyo
- (72) Inventor: Shinsuke Kataoka
 Kayagasaki Dormitory No. 207
 8-1 Moto-machi, Kayagasaki-shi, Kanagawa-ken
- (72) Inventor: Keiko Ehata
 Green Nodi [transliteration] No. 202
 2212-1 Oiso, Oiso-machi, Naka-gun, Kanagawa-ken
- (74) Agent: Takashi Oshima, Patent Attorney
- (54) [Title of the Invention]
 Oral Composition

- (57) [Abstract]

[Objective] To offer an oral composition with high protective and therapeutic effects with respect to periodontal diseases by improving the active oxygen elimination effects of ascorbic phosphate ester and by improving absorption thereof in gingival tissues.

[Constitution] An oral composition, which employs one or more compounds selected from ascorbic acid-2-phosphate ester, ascorbic acid-3-phosphate ester, ascorbic acid-5-phosphate ester, ascorbic acid-6-phosphate ester, ascorbic acid-2-polyphosphate ester, ascorbic acid-3-polyphosphate ester, ascorbic acid-5-polyphosphate ester, ascorbic acid-6-polyphosphate ester and salts thereof, together with one or more compounds selected from menthone, carvone, cineol, limonene, menthane, anethole, eugenol and cinnamic aldehyde, and menthol as necessary.

[Claims]

[Claim 1] An oral composition, characterized by the conjunctive use of ascorbic phosphate ester and one or more [compounds] selected from menthone, carvone, cineol, limonene, menthane, anethole, eugenol and cinnamic aldehyde.

[Claim 2] The oral composition according to claim 1, wherein the ascorbic acid phosphate ester is one or more [compounds] selected from ascorbic acid-2-phosphate ester, ascorbic acid-3-phosphate ester, ascorbic acid-5-phosphate ester, ascorbic acid-6-phosphate ester, ascorbic acid-2-polyphosphate ester, ascorbic acid-3-polyphosphate ester, ascorbic acid-5-polyphosphate ester, ascorbic acid-6-polyphosphate ester and salts thereof.

[Claim 3] The oral composition according to claim 1 or 2, wherein menthol is also used in conjunction.

[Detailed description of the invention]

[0001]

[Field of industrial use] The present invention relates to an oral composition, characterized in that, by using ascorbic acid phosphate ester and specific monoterpenoids or specific phenylpropanoids in combination, the active oxygen elimination effects and gingival tissue absorption of ascorbic acid phosphate ester are improved, thereby improving preventative and therapeutic effects with respect to periodontal diseases.

[0002]

[Prior art and problems to be solved by the invention] Many periodontal diseases are thought to be infections caused by microorganisms, primarily strictly anaerobic Gram-

negative bacilli. Because neutrophil accumulation in periodontal pockets and infiltration of lymphocytes into gingival tissues are observed as characteristic tissue phenomena in chronic periodontal disease, and because serious periodontal disease is found in patients with diseases that cause functional impairment of neutrophils (e.g., diabetes or AIDS), periodontal diseases are now understood to be the result of interactions between defense mechanisms and microbial infection in the body, with an emphasis on neutrophils.

[0003] When bacterial infection is present, neutrophils in the body extravasate from blood vessels, migrate to the site of infection, and kill bacteria by bacterial phagocytosis or releasing active oxygen or lysozomal enzymes, thereby protecting the body from infection. Although the basic function of these neutrophils is to protect the body, when chronic or acute irritation occurs, exudation of cell components or excessive active oxygen production causes damage to body tissues, and exacerbates the infection.

[0004] Thus, research is being investigated into the use of various antioxidants in order to prevent tissue damage resulting from the aforementioned active oxygen. One of these antioxidants is ascorbic acid phosphate ester, and the prevention of periodontal disease using oral compositions produced by blending ascorbic acid phosphate ester antioxidant is disclosed in Japanese Unexamined Patent Application No. Sho 62[1987]-96408.

[0005] However, the active oxygen elimination effects are not that high when ascorbic phosphate ester alone has been used as antioxidant, and in addition, although these effects are strong when ascorbic acid phosphate ester is metabolized in the oral cavity, its absorption with respect to mucous membranes is poor. As a result, the compound cannot reach the disease site, and good effects cannot be manifested.

[0006] The present invention was developed in order to solve the above problems, and has the objective of offering an oral composition that more effectively eliminates active oxygen in infected periodontal tissues, and effectively prevents or treats periodontal diseases.

[0007]

[Means for solving the problems and action] The inventors of the present invention, as a result of painstaking investigations in order to attain the above objectives, arrived at the present invention upon discovering that various active oxygen elimination effects and mucous membrane absorption are synergistically elevated by the conjunctive use of

ascorbic acid phosphate ester and a specific monoterpenoid or specific phenylpropanoid, and in addition, that these results are more effective when menthol is also used in conjunction with the aforementioned substances that are used together.

[0008] Specifically, the present invention offers an oral composition characterized by the conjunctive use of ascorbic phosphate ester and one or more substances selected from menthone, carvone, cineol, limonene, menthane, anethole, eugenol and cinnamic aldehyde.

[0009] To describe the present invention in additional detail, the ascorbic phosphate ester used in the present invention is a derivative having a phosphoric acid group in the 2, 3, 5 or 6-position of ascorbic acid, and examples that may be cited include ascorbic acid-2-phosphate ester, ascorbic acid-3-phosphate ester, ascorbic acid-5-phosphate ester, ascorbic acid-6-phosphate ester, ascorbic acid-2-polyphosphate ester, ascorbic acid-3-polyphosphate ester, ascorbic acid-5-polyphosphate ester, ascorbic acid-6-polyphosphate ester and water-soluble salts thereof. These ascorbic acid phosphate esters may be used individually, or may be used in appropriate combinations of two or more types, but from the standpoint of stability of the composition, it is particular desirable to use ascorbic acid-2-phosphate ester magnesium salt.

[0010] There are no particular restrictions on the blend amount of ascorbic acid phosphate ester in the oral composition of the present invention, but 0.001-10% (wt%, likewise below) with respect to the entire composition is preferred, with 0.01-5% being particularly desirable. If the amount is less than 0.001%, then sufficient effects as an ascorbic acid phosphate ester antioxidant may not be obtained, whereas if the amount exceeds 10%, there may be detrimental effects in terms of sensitivity to the oral composition.

[0011] The oral composition of the present invention is a material wherein one or two substances selected from aforementioned ascorbic acid phosphate esters, specific monoterpenoids and specific phenylpropanoids are used in conjunction.

[0012] The specific monoterpenoid pertaining to the present invention is menthone, carvone, cineol, limonene or menthane, and individual types of these monoterpenoids can be used individually, or two or more types may be used in appropriate combinations. The menthone, carvone, cineol, limonene or menthane may be used as substances that are

isolated from essential oils, as synthesized substances, or as essential oils containing these substances.

[0013] In addition, the specific phenyl propanoids used in the present invention are anethole, eugenol and cinnamic aldehyde. These compound can be used individually, or may be used in appropriate combinations of two or more types. The blend amount of the aforementioned monoterpenoids and phenylpropanoids is 0.0001-5% with respect to the entire composition, with 0.001-1% being particularly desirable. If this amount is less than 0.0001%, there will be cases where the effects are insufficient when used in conjunction with ascorbic acid phosphate ester, whereas if the amount exceeds 5%, there will be cases where detrimental influences will result in terms of sensitivity to the oral composition.

[0014] In the present invention, it is desirable to also blend menthol, since this can increase the active oxygen elimination effects of the ascorbic acid phosphate ester, as well as its absorption with respect to gingival tissues.

[0015] The blend amount of the aforementioned menthol is 0.0001-5% with respect to the entire composition, with 0.001-1% being particularly desirable. If this amount is less than 0.0001%, then there will be cases where the above effects are inadequate, whereas if the amount exceeds 5%, then there will be cases where detrimental influences will result in terms of sensitivity to the oral composition.

[0016] The menthol may be a substance that has been isolated from essential oil, a synthesized substance, or an essential oil containing them.

[0017] The oral composition of the present invention can be used in the form of dentifrices such as toothpaste, mouthwash, gingival massage cream, liquid- or paste-form topical agents, chewing gum and various other dosage forms. In such cases, in addition to the above components, other drug components or various bases used in common dentifrices may also be blended in the oral composition of the present invention.

[0018] With dentifrices, for example, the compound can be obtained by blending one or more substance selected from calcium hydrogen phosphate dihydrate, anhydrous calcium hydrogen phosphate, calcium dihydrogen phosphate, calcium phosphate, calcium carbonate, calcium pyrophosphate, aluminum hydroxide, alumina, anhydrous silicic acid, aluminum silicate, insoluble sodium metaphosphate, magnesium phosphate, magnesium

carbonate, calcium sulfate, polymethyl methacrylate, bentonite, zirconium silicate and synthetic resins (general blend amount: 5-80%, toothpaste: 8-50%).

[0019] In addition, with paste-form oral compositions such as toothpaste, substances that can be blended as binders include one or more substances selected from carrageenan, carboxymethylcellulose sodium, methyl cellulose, hydroxyethyl cellulose, carboxymethylhydroxyethyl cellulose sodium and other cellulose derivatives, arginate, arginic acid propylene glycol ester, xanthan gum, tragacanth gum, karaya gum, gum arabic and other gums, polyvinyl alcohol, sodium polyacrylate, carboxyvinyl polymer, polyvinylpyrrolidone and other synthetic binders, and silica gel, aluminum silica gel, veegum, laponite and other inorganic binders (blend amount: ordinarily 0.1-5% for dentifrices).

[0020] In addition, in the manufacture of dentifrices and other oil-form or paste-form oral compositions, thickeners that can be blended in one or more types include sorbitol, glycerin, ethylene glycol, propylene glycol, 1,3-butylene glycol, polyethylene glycol, polypropylene glycol, xylitol, maltitol and lactitol (blend amount for dentifrices: ordinarily 5-80%).

[0021] Examples of surfactants that may be blended in one or more types are anionic surfactants, nonionic surfactants and amphoteric surfactants (blend amount: ordinarily 0.1-10%, with 0.5-5% being preferred).

[0022] Examples of anionic surfactants that maybe used include sodium lauryl sulfate, sodium myristyl sulfate and other sodium alkylsulfates, sodium N-lauroyl sarcosinate, sodium N-myristoyl sarcosinate and other sodium N-acyl sarcosinates, sodium dodecylbenzenesulfonate, hydrogenated coconut fatty acid monoglyceride sodium monosulfate, sodium lauryl sulfoacetate, sodium N-palmitoylglutamine and other N-acylglutamates, N-methyl-N-acyltaurine sodium, N-methyl-N-acylalanine sodium, sodium α -olefinsulfate and sodium dioctylsulfosuccinate.

[0023] Examples of nonionic surfactants that may be used include sucrose fatty acid esters, maltose fatty acid esters, lactose fatty acid esters and other sugar fatty acid esters, maltitol fatty acid esters, lactitol fatty acid esters and other sugar alcohol fatty acid esters, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monostearate and other polyoxyethylene sorbitan fatty acid esters, polyoxyethylene hardened castor oil and other

polyoxyethylene fatty acid esters, lauric acid mono- or diethanolamide, myristic acid mono- or diethanolamide and other fatty acid ethanolamides, sorbitan fatty acid esters, fatty acid monoglycerides, polyoxyethylene higher alcohol ethers, polyoxyethylene polyoxypropylene copolymers and polyoxyethylene polyoxypropylene fatty acid esters.

[0024] In addition, examples of amphoteric ionic surfactants that may be used include N-lauryl diaminoethyl glycine, N-myristyl diaminoethyl glycine and other N-alkyl diaminoethyl glycine, N-alkyl-N-carboxymethylammonium betaine, and 2-alkyl-1-hydroxyethylimidazoline betaine sodium.

[0025] Substances that may also be blended in the oral composition of the present invention include sodium saccharin, stevioside, neohesperidin dihydrochalcone, glycyrrhizin, perillartine, thaumatin, aspartylphenylalanine methyl ester, p-methoxycinnamic aldehyde and other sweeteners, preservatives and fragrances. For example, with toothpastes, the composition can be manufactured by blending the aforementioned desired components with an appropriate amount of water.

[0026] In addition, when other oral compositions are to be manufactured, appropriate components that are commonly employed may be used, and manufacture can be carried out by common methods.

[0027] In the present invention, one or more types of well-known effective components may be blended, such as chlorhexidine, benzetonium chloride, benzalkonium chloride, cetylpyridinium chloride, decalinium chloride and other cationic antimicrobial agents, triclosan, hinokitiol, biosol and other phenolic compounds, dextranase, mutanase, lysozyme, amylase, protease, lytic enzymes, superoxide dismutase and other enzymes, sodium monofluorophosphate, potassium monofluorophosphate and other alkali metal monofluorophosphates, sodium fluoride, stannous fluoride and other fluorides, tranexamic acid, epsilon-aminocaproic acid, aluminum chlorohydroxy allantoin, dihydrocholestanol [*sic*, possibly “dehydrocholestanol” or “dihydrocholesterol”], glycyrrhizic acid, glycyrrhetic acid, bisabolol, glycerophosphate, chlorophyll, sodium chloride and water-soluble inorganic phosphoric acid compounds.

[0028]

[Effect of the invention] The oral composition of the present invention involves the conjunctive use of ascorbic acid phosphate ester and specific monoterpenoids or

phenylpropanoids, and by this means, improves the mucous membrane absorption of the ascorbic acid phosphate ester, while also effectively eliminating excessive active oxygen produced as a result of defense mechanisms. The composition is thus useful in the prevention and treatment of gingival tissue breakdown in periodontal disease.

[0029]

[Working examples] Experimental examples and working examples are presented below in order to describe the present invention in additional detail. However, the present invention is not restricted to the following working examples.

[0030] (Experimental Example 1) Experiment concerning active oxygen elimination

2% Casein was introduced intraperitoneally into mice, and after 16 h, the extracted peritoneal cells were washed with HBSS, and prepared at 2.5×10^6 cells/mL. 50 μ L quantities of the solutions indicated in Table 1 were introduced as drugs into 50 μ L of peritoneal cell suspension, and the cells were incubated for 5 min at 35°C. 100 μ L of luminol solution and 50 μ L of *Porphyrromonas gingivalis* 381 suspension ($OD_{550} = 1.0$) were then added, and after incubating for 5 min, the resulting activated oxygen was measured with a lumiphotometer.

[0031] Results concerning the active oxygen inhibitory actions of the various agents are compiled in Table 1. In Table 1, APM denotes ascorbic acid phosphate ester magnesium salt (likewise below), and the various drug concentrations when using the other drugs in combination with APM are the same as when using the drugs alone.

[0032]

[Table 1]

Drug	Active oxygen production (rlu)	Inhibition (%)
Control	751	--
APM (10 μ M)	557	25.8
Menthol (1 μ M)	683	9.0
Carvone (1 μ M)	710	5.4
Menthone (0.1 μ M)	696	7.3
Cineol (1 μ M)	697	7.3
Limonene (1 μ M)	687	8.5
APM + carvone	436	42.0
APM + menthone	416	44.6
APM + cineol	454	39.6
APM + limonene	448	40.3
Anethole (1 μ M)	689	8.2
Eugenol (1 μ M)	692	7.9
APM + anethole	441	41.3
APM + eugenol	421	43.9

APM + carvone + menthol	206	72.6
APM + menthone + menthol	195	74.0
APM+ cineol + menthol	241	67.9
APM + limonene + menthol	238	68.3
APM + anethole + menthol	223	70.3
APM + eugenol + menthol	215	71.4

[0033] From the results of Table 1, it was found that active oxygen is synergistically removed when ascorbic acid phosphate ester is used in conjunction with carvone, menthone, cineol, limonene, anethole and eugenol. In addition, when menthol is added in addition to these conjunctively used substances, additionally effective elimination of active oxygen is produced.

[0034] (Experimental Example 2) Experiment concerning improvement in rat gingivitis

ODU rats (7-weeks) were used as the experimental animals, and the rats were reared for 2 months on powdered food so that dental plaque accumulated in the lower incisor region, thereby experimentally inducing gingivitis. 5 animals were used per group (day 0), and a gel produced by blending the drugs indicated in Table 2 (day 0) was applied with a spatula to two locations on the left and right gingival tissue in the lower incisor region for a period for 20 days. The infected gingival tissue surface area was measured by stereoscopic microscopy on day 0 and day 20, and the improvement in infection was determined using the formula below.

Gingivitis improvement (%) = $(A-B) \times 100/A$

A: Infected surface area at day 0

B: Infected surface area at day 20

The results for rat gingivitis improvement effects obtained with the various drugs are compiled in Table 2.

[0035]

[Table 2]

Drug	Gingivitis improvement (%)
Control (base only)	2.1
APM (0.2%)	14.1
Menthol (0.1)	3.3
Carvone (0.1%)	2.0
Eugenol (0.1%)	2.6
APM (0.2%) + carvone (0.1%)	28.2
APM (0.2%) + eugenol (0.1%)	27.9
APM (0.2%) + carvone (0.1%) + menthol (0.1%)	41.2

APM (0.2%) + eugenol (0.1%) + menthol (0.1%)	40.7
--	------

[0036] From the effects of Table 2, it was found that the ascorbic acid phosphate ester and carvone or eugenol, when used in conjunction, act synergistically to improve gingivitis. It was also found that when menthol is used in conjunction with these two compounds, gingivitis can be more effectively improved.

[0037] (Experimental Example 3) Experiment concerning the stimulation of mucous membrane absorption

25 mL of ascorbic acid phosphate ester magnesium salt (10 mM), a mixture of this substance together with carvone (5 mM) or eugenol (5 mM), or a mixture produced by the addition of menthol thereto, was incubated for 5 min at 37°C, whereupon the mixture was gargled in the oral cavity for 5 min. The mixture was then expectorated into a beaker. The oral cavity was rinsed for 5 sec with 10 mL of distilled water and this volume was added thereto, whereupon the total volume was adjusted to 50 mL. This solution was then centrifuged for 10 min at 3000 xg, whereupon the supernatant was collected and subjected to HPLC analysis under the conditions described below in order to quantify the results.

HPLC analysis conditions:

Column: Shiseido CAPCELL PAK AG-120 (0.6 x 25 cm)

CAPCELL PAK AG-120 (0.6 x 3.5 cm)

Mobile phase: 0.1 M KH₂PO₄/0.1 M H₂PO₄ (pH 2)

Detector: 240 nm

Rate: 0.7 mL/min

Results concerning the effects of the various drugs on acceleration of mucous membrane absorption are presented in Table 3.

[0038]

[Table 3]

Drug	Mucous membrane absorption (%)
APM (10 mM)	5.2
APM (10 mM) + carvone (5 mM)	19.8
APM (10 mM) + eugenol (5 mM)	15.7
APM (10 mM) + carvone (5 mM) + menthol (5 mM)	26.3
APM (10 mM) + eugenol (5 mM) + menthol (5 mM)	25.1

[0039] From the results of Table 3, it was confirmed that carvone and eugenol stimulate mucous membrane absorption of ascorbic acid phosphate ester magnesium salt. In addition, it was found that when menthol is also blended, the mucous membrane absorption of ascorbic acid phosphate ester magnesium salt is further accelerated.

[0040] Working examples are presented below.

[Working Example 1] Toothpaste

Sedimented silica	25.0%
Sorbitol	25.0
Glycerin	25.0
Polyvinylpyrrolidone	1.0
Lauroyl polyglycerin ester	1.0
Polyoxyethylene (60) sorbitan monolaurate	0.5
Sodium saccharin	0.2
Ethyl paraoxybenzoate	0.1
Chlorhexidine hydrochloride	0.1
Ascorbic acid phosphate ester magnesium salt	0.1
Carvone	0.05
Menthol	0.1
Fragrance	1.0
Water	remainder
	Total 100.0%

[0041]

[Working Example 2] Toothpaste

Calcium hydrogen phosphate dihydrate	20.0%
Anhydrous calcium hydrogen phosphate	20.0
Gelled silica	2.0
Sorbitol	20.0
Propylene glycol	2.5
Carboxymethylcellulose sodium	1.0
Lauryl diethanolamide	1.0

Sodium lauryl sulfate	1.5
Lauroyl sarcosine sodium	0.9
Sodium saccharin	0.1
Ethyl paraoxybenzoate	0.1
Ascorbic acid phosphate ester magnesium salt	0.05
Menthol	0.1
Eugenol	0.05
Fragrance	0.8
<u>Water</u>	<u>remainder</u>
Total	100.0%

[0042]

[Working Example 2] Toothpaste

Cetanol	5.0%
Squalane	20.0
Precipitated silica	5.0
Polyoxyethylene (40) modified castor oil	0.1
Sorbitan monooleate ester	1.0
Sodium lauryl sulfate	0.2
Glycyrrhizic acid	0.1
Sodium saccharin	0.6
Ascorbic acid phosphate ester	0.2
Menthol	0.2
Carvone	0.1
Fragrance	0.6
<u>Water</u>	<u>remainder</u>
Total	100.0%

[0043]

[Working Example 3] Oral paste

Liquid paraffin	15.0%
-----------------	-------

Cetanol	7.0
Glycerin	20.0
Sorbitan monopalmitate	0.6
Polyoxyethylene (40 mol) sorbitan monostearate	5.0
Sodium saccharin	0.5
Cetylpyridinium chloride	0.05
Ascorbic acid phosphate ester	0.5
Menthol	0.2
Anethole	0.05
Fragrance	0.5
Water	<u>remainder</u>
Total	100.0%

[0044]

[Working Example 5] Mouthwash

Sorbitol	10.0%
Ethanol	5.0
Polyoxyethylene (60 mol) hardened castor oil	0.1
Sucrose monopalmitate	0.2
Sodium saccharin	0.2
Triclosan	0.03
Cetylpyridinium chloride	0.05
Ascorbic acid phosphate ester	0.05
Cinnamic aldehyde	0.1
Carvone	0.1
Fragrance	0.6
Water	<u>remainder</u>
Total	100.0%

[0045]

[Working Example 6] Chewing gum

Gum base	20.0%
Sugar	15.0

Isomaltose	20.0
Paratinose	20.0
Corn syrup	12.0
Malt syrup	11.9
Ascorbic acid phosphate ester	0.02
Limonene	0.1
Menthone	0.03
<u>Fragrance</u>	<u>0.6</u>
Total	100.0%

[patent revisions listed have already been incorporated]



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60/263,884

01/24/2001

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CONFIRMATION NO. 4106

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OC000000005891896

JOHN P. IWANICKI
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Applicant(s)

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Non-Publication Request: No

Early Publication Request: No

Title

Mouth wash

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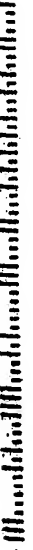
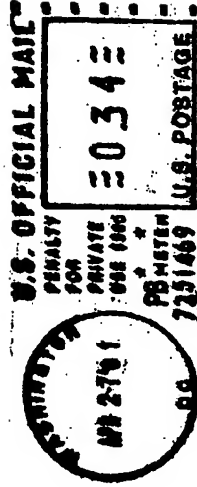
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MOUTH WASH

The addition of ascorbyl phosphate esters and their salts, such as the trisodium salt of ascorbyl-2-monophosphate, to toxicologically acceptable oral carriers results in useful oral care compositions that may be used to counteract tooth decay, prevent tooth stain accumulation and assist in the regenerative process of periodontal tissues. The inventive compositions may also include a source of calcium ions in order to encourage the precipitation of one or more forms of calcium phosphate during use. Compositions containing both an ascorbyl phosphate ester and a calcium ion source may have utility in the remineralization of tooth enamel, useful in the reversal of such early stage oral hard tissue disease processes such as primary root caries lesions.

Application of the inventive compositions may be accomplished by brushing, rinsing, spraying, chewing, swabbing, adhering or otherwise applying said compositions to one or more oral tissue surfaces. Application may also be made by placing an ascorbyl phosphate ester containing composition, for instance a gel, into a dental tray and attaching the tray to the maxillary (upper) and/or mandibular (lower) arch of teeth so that the teeth make contact with the gel inside the tray.

Example 1

Mouthwash composition with sodium ascorbyl-2-monophosphate

Ingredient	Percent (w/w)
Deionized water	86.190
Glycerin	7.500
Sodium tripolyphosphate	3.000
Polyethylene glycol 8000	1.000
Sodium saccharin	0.060
Sodium benzoate	0.500
Sodium ascorbyl-2-monophosphate	1.000
PEG-60 hydrogenated castor oil	0.600
Flavor	0.150
Total	100.000

The above composition had a pH of 8.86, a specific gravity of 1.058, and a refractive index of 1.3530.

Example 2

Prophetic toothpaste example with sodium ascorbyl-2-monophosphate

Ingredient	Percent (w/w)
Deionized water	17.298
Sodium ascorbyl-2-monophosphate	0.500
Sodium benzoate	0.500
Sodium fluoride	0.240
Titanium dioxide	1.200
Sodium saccharin	0.400
Sorbitol (70% solution)	34.562
Glycerin	18.000
Cellulose gum	1.000
Hydrated silica (abrasive)	17.500
Hydrated silica (thickener)	7.000
Sodium lauryl sulfate	1.000
Flavor	0.800
Total	100.0000

The following chart is a summary of the approximate range of concentrations (on a weight percent basis) for components of mouthwash and toothpaste compositions containing the inventive ascorbyl phosphate. The term ascorbyl phosphate will for the purposes of this disclosure mean one or more phosphate esters of ascorbic acid, either alone or in combination. The term ascorbyl phosphate shall also mean any corresponding inorganic or organic salts of phosphate esters of ascorbic acid. The preferred ascorbyl phosphate is ascorbyl-2-monophosphate and the most preferred ascorbyl phosphate is the trisodium salt of ascorbyl-2-monophosphate, also known simply as sodium ascorbyl phosphate.

Component	Mouthwash	Toothpaste / Gel
Water	46 - 99.9	0 - 99.89
Ascorbyl-2-phosphate	0.01 - 10	0.01 - 10
Fluoride source	0 - 1	0 - 1
Preservative	0 - 3	0 - 3
Humectant	0 - 30	0 - 70
Artificial sweetener	0 - 1	0 - 2
Thickener / binder	0 - 5	0.1 - 20
Surfactant	0 - 5	0 - 5
Abrasive	0	0 - 60
Pigment / Dye	0 - 0.2	0 - 5
Flavorant	0 - 2	0 - 3

Ascorbyl phosphates may also be added to other types of oral care compositions, as well as certain types of foodstuffs, including, but not limited to, chewing gum, dental floss, tooth whitening gels and pastes, breath sprays, buccal patches, medicament delivery strips, and lozenges. Any device or carrier for delivery of ascorbyl phosphate to hard and/or soft tissue surfaces in the oral cavity is contemplated to be within the scope of this invention.

Also contemplated is the inclusion of a phosphatase enzyme inhibitor, such as a fluoride ion source, in the inventive ascorbyl phosphate-containing compositions. Other auxiliary oral care ingredients, such as those employed for tartar control, tooth bleaching or whitening, halitosis elimination or prevention, and microbial control, may also be included. Also, one or more means of retaining the ascorbyl phosphate on hard or soft tissue surfaces for extended periods of time (for instance, in excess of one hour) are contemplated. Such retention means may include a polymer.

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Washington, D.C. 20231

Applicant: R. Eric Montgomery

USSN: TBA

Title: TOPICAL ORAL CARE COMPOSITIONS

Atty. JPIwanicki

Docket No.: 04163-00139

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☒ Transmittal Letter 3 pages
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 Drawings [] formal [] informal sheets
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